PowderJect Technologies photo

Special Delivery

Alternative methods for delivering drugs improve performance, convenience, and patient compliance

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The active ingredient in a medicine is only part of the arsenal against disease. The drug must somehow get to the right place at the right time. That's where drug delivery comes in.

Drug delivery companies work to devise new dosage forms for medications. Historically, this has meant product lifecycle management, a process in which a pharmaceutical company looks for ways to set apart a product reaching the end of its patent lifetime from the inevitable generic competition. For example, a company might tinker with a drug that patients must take multiple times a day and reduce that to a single dose.

Extending the patent life, however, "is not enough if you're not really adding value," says Ron Haak, senior vice president of technology development at Alza Corp., Mountain View, Calif. "If a prescriber or a patient has a choice between a low-cost generic or an expensive patented drug that offers no real advantage, they'll take the low-cost generic. Nowadays, the competition is so intense in the pharmaceutical marketplace that companies look to drug delivery as a way to gain a competitive advantage." The value that drug delivery adds can be improved safety, efficacy, convenience, and patient compliance.

From Wall Street's point of view, this older approach to drug delivery technologies has become "commoditized," says Corey Davis, a financial analyst at Chase H&Q, New York City. He says the interest now is in "more exotic drug delivery platforms" for molecules such as proteins. The biggest problem with proteins as drugs is that they are difficult to deliver orally. Almost every therapeutic protein currently on the market is delivered by injection.

Many people believe that proteins are going to comprise an increasing proportion of the new-drug market. In addition, Joseph R. Robinson, a professor of pharmaceutical chemistry at the University of Wisconsin, Madison, points out that many existing peptide and protein drugs are coming off patent, fueling the interest in developing new dosage forms. "There is the equivalent of a generic industry that will likely be developed for peptides and proteins, analogous to [what evolved with] small molecules," he says.

The typical business model for drug delivery companies is to form partnerships or collaborations with pharmaceutical companies. The drug delivery company develops the new dosage form and receives royalties or milestone payments from the pharmaceutical company.

The race is on to develop alternatives to injection for macromolecules. The main methods being explored are pulmonary (inhalation) and oral formulations. In addition, transdermal and extended-release injectable formulations are being targeted. The technologies described in this article are just a sampling of the drug delivery techniques that are being developed.

Take a deep breath

Pulmonary delivery isn't just for bronchodialators and other asthma medications anymore. Several drug delivery companies are developing technologies

for systemic delivery of proteins and other macromolecules through the alveoli of the lung. Of the various alternatives to injection for the administration of proteins, pulmonary delivery is probably the closest to a commercial reality.

Pulmonary delivery companies are trying to replace the injections that are currently used to administer most therapeutic proteins. For example, Inhale Therapeutic Systems, San Carlos, Calif., is collaborating with Biogen, Cambridge, Mass., to develop a pulmonary version of Avonex, interferon β-1a used to treat multiple sclerosis. Avonex is given as a painful intramuscular injection, according to Andrew R. Clark, vice president for scientific affairs at Inhale. "Even though it's once a week, the patients almost dread taking it," he says. Pulmonary administration is attractive because it is noninvasive.

In addition, the lungs provide rapid absorption into the bloodstream, which is sometimes faster than subcutaneous injections. "The total surface area of the lung is about the size of a tennis court in a normal adult," says Igor Gonda, chief scientific officer at Aradigm, Hayward, Calif. "In a single inhalation, you can access this large surface area, one that is also very absorptive."

Although absorption in the lungs is rapid, it tends to be less efficient than injections, Clark notes. For example, he says, "the bioavailability of inhaled insulin is somewhere between 10 and 15% of what it would be if it were an injection." Therefore, the device used to deliver drugs to the lung must be as efficient as possible.

According to Gonda, the only limitation for pulmonary systemic delivery of small molecules—such as morphine—is the efficiency of delivery. For larger molecules, he says, "the biology takes over." The body clears such molecules from the lungs by several mechanisms, including metabolism and phagocytosis (uptake by white cells known as phagocytes), which compete with absorption. "The way people breathe during the delivery of inhalation products has profound importance for the deposition of the drug in the lung and therefore ultimately for absorption," he says. "The deeper into the lung that you deposit the drug, the more of it is going to be absorbed into the systemic circulation."

Unfortunately, the efficiency of pulmonary delivery depends greatly on coordination of the patient's breathing with the actuation of the delivery device. In addition, aerosols leave traditional inhalers so quickly that much of the medicine can't negotiate the bends of the airway and

New materials for drug delivery

Sometimes the answer to a drug delivery problem is to invent a new biomaterial.

Chemical engineer Mark E. Davis of California Institute of Technology set out to rationally design a new polymer system for the delivery of plasmids (rings of DNA not on chromosomes) for gene therapy. He needed something that was nontoxic (so it wouldn't cause an immune response) that could bind and condense DNA. "Based on that criteria, we came up with the idea of trying to create a linear polymer that contained cyclodextrin in the backbone," Davis says.

Davis subsequently has constructed a number of polymers, which differ in length, charge, and flexibility [*Bioconjugate Chem.*, 10, 1068 (1999)]. Polymers that are suitable for nucleic acids tend to be short and positively charged. Davis says he was attracted to cyclodextrins because they are well tolerated in humans. The idea was to use these benign molecules as building blocks for polymers that would interact with DNA and provide composite particles that maintain the advantageous properties of cyclodextrins.

Davis' polymers have in fact been relatively nontoxic. The toxicity is associated with the charged portions that connect the cyclodextrins. "By adjusting the chemistry, we can tune the charge in and out," Davis says. "We can show that the toxicity is not coming from the cyclodextrin part of the polymer but from the charged part."

The spacing of the charges makes a big difference in the performance of the polymers. "Just small angstrom changes between the two charges have significant effects on binding and delivering DNA," Davis says.

Davis' group has shown that the polymers can deliver genes over a variety of cell lines in vitro. Initial studies with animal models currently are under investigation, and preliminary results are encouraging, Davis says. A company, Insert Therapeutics, has been created to develop the polymers for commercial purposes.

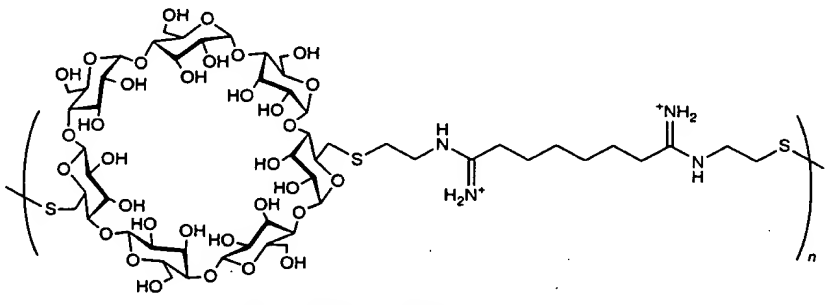
More work is necessary, however, to understand the mechanism of the gene delivery process. "If I don't know what the mechanisms are, it's hard to know exactly what to do next as far as tuning the material," he says.

Meanwhile, assistant chemistry professor Mark W. Grinstaff and graduate student Geoffrey S. Hird at Duke University have developed a material that is a twist on conventional liposomes, which are made of glycerol-based phospholipids. In Grinstaff's material, the glycerol has been replaced with ribose [*J. Am. Chem. Soc.*, 122, 8097 (2000)]. Grinstaff calls the resulting supramolecular structures "carbohydrosomes."

"This carbohydrate backbone allows us to perform additional structural modifications," Grinstaff notes. "We can attach ligands for targeted drug delivery, cationic groups for gene delivery, or probes for diagnostic uses." Conventional lipids are modified at the head group, whereas this novel lipid can be modified at the backbone as well as the head group.

Besides the opportunity for chemical derivatization, the supramolecular structures form a more stable liquid-crystalline phase below a transition temperature. Above this temperature, a fragile and more permeable structure exists. "You may be able to manipulate the system for efficient drug delivery release when you go through a phase transition," Grinstaff says.

The work on the carbohydrasomes is still at a preliminary stage. "We have a lot to learn about this unique supramolecular structure and its potential biotechnological applications," Grinstaff acknowledges.



Cyclodextrin-containing comonomer

ends up driven into the back of the throat. The pulmonary delivery companies have developed devices to improve the efficiency of delivery and take much of the guesswork from the patients.

Inhale's device has a pump unit that atomizes the medication, which is in a powder form, to make an aerosol. "Instead of trying to rely on the patient to actuate the device and synchronously inhale, you actuate the device and the aerosol cloud is put inside a chamber," Clark says. "The patient can inhale from the chamber. You don't get misdosing because you are not able to coordinate properly."

The chamber holds a couple hundred milliliters of air, whereas the typical inspiration of an adult is approximately 700 mL. The high velocity necessary to form the aerosol dissipates in the chamber rather than going into the patient's mouth, Clark says.

Aradigm also has developed a delivery device that has red lights and green lights to help coach patients to better coordinate the timing and speed of a breath while actuating the device. This greatly affects the efficiency of the delivery. The device measures inspiratory flow rate with a pressure transducer.

Dura Pharmaceuticals, San Diego, has developed a system known as Spiros that uses electromechanical energy to form the aerosol from the powdered drug. "By using the battery, the motor, and the switch, we can actually convert the energy from the batteries into energy for dispersion of the powder," says Robert K. Schultz, vice president for technology, strategy, and partnering. "The patients then simply breathe slowly and comfortably and achieve an efficient dose to the lungs."

A second-generation device called Spiros S2 does not use a motor. Instead, free-floating beads in a chamber create the dispersion. "The aerosol itself is essentially formed by the disaggregation of the powder in the airflow path," Schultz says. The combination of the patient's breath and the bead motion in the chamber causes the powder to be dispersed.

Dura Pharmaceuticals uses a simple formulation, consisting of milled powders blended with lactose as a bulking agent. "We've not had to use complicated or more sophisticated formulation technologies," Schultz says. The system was originally designed for small molecules and has also been applied to proteins. "Sometimes, for macromolecules, we find that if we're looking for systemic delivery we will mill the powders to have more material" in the size range of 1 to 3 μm, he says.

Several types of inhalant devices are under development: Clockwise from above, Aradigm's inhaler helps coach users for more efficient delivery; Dura Pharmaceuticals' device uses beads to generate an aerosol; and Inhale Therapeutics' inhaler creates an aerosol in a chamber for easier dosing.

One of the areas that Dura has been focusing on is pulmonary delivery of vaccines. Schultz says the company has a publicly announced collaboration with the World Health Organization for a measles vaccine. And last week, Dura and Elan Corp., Dublin, Ireland, announced that they have entered a merger agreement under which Elan will acquire Dura.

Inhale uses proteins that are in a powder form. However, most proteins currently used for therapy are administered in a liquid solution. To be used with Inhale's device, the proteins must remain stable in the solid state—that is, they must maintain the right shape and chemical structure to be biologically active. That means the formulation must somehow replace the interactions in the proteins' normal aqueous environment.

To provide the stability that the proteins need, Inhale uses a glass technology. Molecules in the powder particles don't have a crystalline structure and are randomly oriented. Interactions between the excipients—ingredients in the formulation other than the drug molecule—and the protein stabilize the protein, Clark explains. But the formulation is a solid rather than a liquid. This is accomplished by making the glass transition temperature much higher than room temperature.

"You get a product that will keep the molecules stable and will remain physically stable when patients leave it on the table, carry it in their pockets, or put it in their cars," Clark says. Inhale calls the particles from the glass-forming mixture PulmoSols.

Inhale has a second technology calle PulmoSpheres, which it acquired last No vember from Alliance Pharmaceuticals San Diego. These particles are formed b spray drying an emulsion of water, per fluorocarbon, and lipids. The particles ar made from water droplets containing th lipid-encapsulated perfluorocarbon. Whe the water is driven off, the lipid and th drug in the aqueous solution solidify. Afte the particles set, the perfluorocarbon eva orates and leaves holes in the particles.

"You end up with a particle that look a little bit like swiss cheese," Clark say He explains that the holes make it easier t blow the particles apart and make an aer sol. Clark suggests that PulmoSpheres w be useful in metered-dose inhalers—th more familiar asthma inhalers.

The new hydrofluoroalkanes used a propellants in metered-dose inhalers f the pores and create a stable suspensio However, metered-dose inhalers man factured with the new propellants, whic have replaced chlorofluorocarbons, ha notoriously poor dose uniformity. A though this wouldn't normally be a cli cal problem for asthma medications b cause they have large "therapeutic wi dows" (ranges at which they provi therapeutic effect), dose uniformity h come under increasing scrutiny from t

world's regulatory authorities, according to Clark.

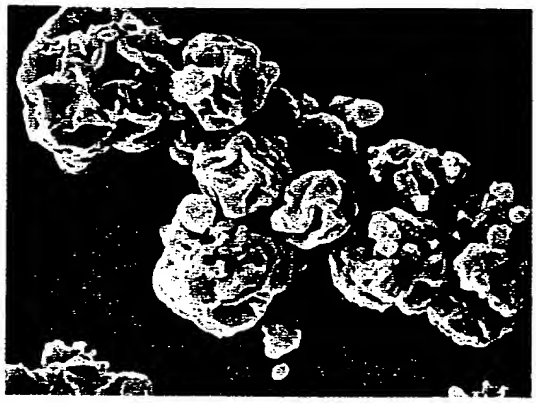
Inhale's lead product is insulin, which is being developed in collaboration with Pfizer, New York City. The product is currently undergoing Phase III clinical trials.

Dura also has an inhalable form of insulin in development. The project is being undertaken in collaboration with Eli Lilly & Co., Indianapolis. The product is in Phase II clinical trials.

For insulin, patients need to be able to adjust the dose. Clark says that will be accomplished by using blister packs with different doses of insulin. The needed dose would be administered by mixing and matching the blister packs.

Aradigm uses liquid formulations, primarily aqueous, for its pulmonary delivery systems. "Our sterile liquid formulation approach leverages from the formulations that are already used for administration by injection," Gonda says.

Aradigm is also working on an inhalable form of insulin. Gonda believes that the introduction of inhaled insulin will open new markets for insulin among Type II (non-insulin-dependent) diabetics, who have previously refused insulin therapy because they don't want to inject themselves. "Insulin would be the best therapy for many of them," he says. "With our system that uses single-dose disposable packets, the patients will be able to dial on our AERx device how many units of insulin they would like to administer. Most patients should be able to get their mealtime dose of insulin from a single packet."



Inhale Therapeutics uses glass technology to create PulmoSol particles (shown) for pulmonary delivery of solid proteins.

Alkermes, located in Cambridge, Mass., is developing a technology that goes against the conventional wisdom of pulmonary delivery. Rather than making small particles, Alkermes makes larger particles that behave in an airstream like smaller particles, says James M. Frates, vice president and chief financial officer. Alkermes acquired the technology when it purchased Advanced Inhalation Research (AIR) in February 1999.

"The discovery at AIR was that you could make large porous particles that behave in an airstream like a 1- to 3-μm particle," Frates says. "We make particles that are 5 to 30 μm that are like crumpled-up pieces of paper. They are porous and extremely light. Since these particles are much less dense than traditional particles, they behave the same in an airstream [as the smaller particles]." Frates uses the analogy of popped versus unpopped popcorn to ex-

plain the difference between the AIR particles and other particles.

He says the forces holding the larger particles together are weaker than those holding smaller particles. Therefore, the larger particles can be dispersed in a repeatable way with less energy, he says, using a simple device that is powered only by a patient's breathing.

The AIR particles also have the potential for sustained release, according to Frates. "We're talking about particles that can last six to 24 hours in the lungs," he says. Alkermes has demonstrated sustained release in animal models and is working with the asthma drug albuterol in human trials.

Another drug that could benefit from sustained release is insulin. The real opportunity for pulmonary delivery of insulin will be fully realized, Frates says, when long-acting insulin is available that can control glucose levels overnight.

Through the skin

PowderJect Technologies, Fremont, Calif., has developed a technology that could be considered a hybrid of transdermal and parenteral (injection): a needleless injection. The company's device propels powder drugs with a supersonic jet of helium gas.

Terry L. Burkoth, PowderJect senior vice president of science and technology, explains that when a high-pressure ampule of helium within the device is broken open, the gas flows through a cassette that is holding the powder between two membranes. The membranes rupture and the gas stream picks up the particles. The particles are propelled fast enough to penetrate the stratum corneum, the outer layer of the skin. The drug is targeted to the boundary between the epidermis and the dermis. Drugs then dissolve and either reach systemic circulation or exert a local effect. Vaccines can be picked up by antigen-presenting cells in the epidermis or by the lymph system.

PowderJect's technology requires that the formulation be a powder. However, those few drugs that are in a liquid state when pure can also be delivered if they are suitably formulated or adsorbed on a carrier particle, Burkoth says. Because the delivery is driven by momentum, Burkoth says the particles, which are between 20 and 70 μm, should be as dense as possible. "The higher the density, the more momentum, given the velocity that we impart to the particles," he says. The particles also must be strong because they hit the skin at high velocities. Burkoth says the particles have been clocked as fast as 900 meters per second, with 400 to 600 meters per second being the more typical range.

What does it feel like to have particles penetrating the skin at such high speeds? Burkoth says the process is completely painless. "People feel the tap of the gas on the skin. It's like flicking your finger against your skin." Clinical trials indicate that the gas is causing the sensation, because patients can't tell if there is powder in the cassette.

The stratum corneum is affected, however. The flux of water across the skin is increased for as long as 24 hours after an injection. Because of that increased permeability, PowderJect has successfully completed early clinical trials exploring the technique to extract analytes from the skin for such applications as glucose monitoring, Burkoth says.

The gas does not actually penetrate the skin. Instead, it is reflected back into the device through a silencer. The silencer is necessary because the flow is transiently supersonic. Instead of hearing a report, the sound is like a gentle handclap, Burkoth says.

One limitation of PowderJect's method is the amount of drug that can be delivered, Burkoth says. The upper threshold is about 3 mg, with 1 to 2 mg preferred. This limits the application to potent drugs, but most commercially attractive biotechnology drug molecules and vaccines fall in this range, Burkoth says. "The ideal candidate is something that is now delivered by needle and syringe," he notes.

Drugs delivered with PowderJect's technology reach the circulatory system faster than those administered by subcutaneous injection. "Because it's an intradermal delivery and the capillary blood supply is immediately adjacent to where you're placing the drug, in most cases—all the cases we've looked at so far—the drug appears in the systemic circulation a bit sooner. Not as fast as [intravenous], but definitely faster than subcutaneous needle and syringe, which is what we compare ourselves to," Burkoth explains.

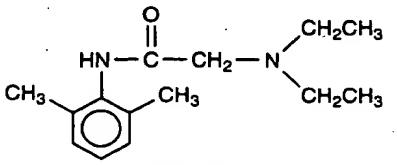
The company has engineered all control of the delivery into the device, Burkoth says. "It has an interlock, so it

has to be pressed [against the skin] with a certain amount of force before you can press the button to release the gas," he comments.

PowderJect is focusing on vaccines because the technology delivers the vaccines more directly to antigen-presenting cells. "We put our particles right there in the epidermis where they're desired," Burkoth asserts. "Either for traditional vaccines, which are protein subunits or killed viruses, or DNA vaccines, which are plasmids on gold, we're delivering automatically to the most sensitive tissue."

However, the product that PowderJect is using to initially prove the technology is the local anesthetic lidocaine hydrochloride, which is a small-molecule drug. That drug must be used anywhere on the body it's needed. "We've tested all over the body," Burkoth says. "For delivery of a drug, just like with patches, we would recommend a site for each specific application."

Alza is another company that is developing technologies to deliver drugs through the skin. One of these technologies, called E-Trans, uses electrical current to deliver drugs across the skin, a process known as iontophoresis. The lead product is for the on-demand delivery of fentanyl, an opioid analgesic used for the treatment of acute pain, Haak says.



Lidocaine

When a patient pushes a button on the device, current flows between two electrodes. "As current flows, we get a predetermined amount of drug injected into the body. That gives us a very reliable way of delivering a particular amount of drug into the body," Haak says. "When this product hits the marketplace, I believe people will be very surprised at the degree of control and the speed with which the compound can be transported through the skin."

Alza is also developing what it calls Macroflux technology, which incorporates a thin titanium screen with microprojections to create mechanical pathways for drug transport. It expands the range of drugs amenable to transdermal delivery to include small hydrophilic molecules and macromolecules. It can be incorporated with the E-Trans technology or more traditional transdermal patches. One simple prototype in early exploration involves a Macroflux system where the projections have been coated with the therapeutic agent, such as a macromolecule. After application, the agent is rapidly absorbed into the skin.

Sontra Medical, Cambridge, Mass., is developing ultrasound as a way to enhance transdermal drug delivery. The application of ultrasound to the skin increases the skin's permeability. The company's SonoPrep system, which is still an investigational device, is based on technology developed by Robert S. Langer, a professor of chemical and biomedical engineering at Massachusetts Institute of Technology, and coworkers.

Langer also is working on develop-

ing microchip drug delivery devices (C&EN, Feb. 1, 1999, page 30). A company—MicroCHIPS in Cambridge, Mass.—has been formed to commercialize the technology.

Making injections friendlier

Although many companies proclaim their delivery technologies are a way to avoid the needle, sometimes the needle is called for. Elan Pharmaceutical Technologies, Dublin, Ireland, has a technology that tries to make injections patient-friendly. The technology, known as Medipad, is best described as "a pump that you wear like a patch," says Larry Sternson, president of Elan Pharmaceutical. The device is worn by the patient on the chest, back, or abdomen.

The device is a small, plastic gas-driven pump with an adhesive backing. The adhesive is used to attach the device to the patient's body, and a button is pressed. "When you push that button, a needle is deployed, which enters the subcutaneous space and then delivers drug at a constant rate until the entire content of the reservoir is expended," Sternson says. He claims that the device has both convenience and compliance advantages: convenience because the patient can go about regular activities and compliance because once the device is attached, the drug is infused at a constant rate unless the device is deliberately removed.

The first applications for this device will be in chronic pain management and in the delivery of macromolecules that have inherently short biological half-lives, Sternson says. Later versions will incorporate control of the delivery profile as well as delivery of boluses, as necessary.

SkyePharma, San Diego, has developed a technology called DepoFoam for extended-release injectable drugs. The spherical particles contain what Randall C. Willis, director of new product development, calls a discontinuous water phase in which droplets are separated from each other.

DepoFoam particles are divided into nonconcentric chambers by bilayer lipid membranes. The membranes are synthetic versions of biological membranes that contain phospholipids, cholesterol, and triglycerides.

The particles are formed by a double emulsion process. The drug is placed in an aqueous solution. That solution is mixed with an oil phase to form an emul-

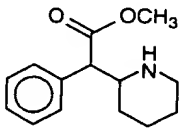
Engineering a new drug delivery profile

Most of the excitement in drug delivery may involve proteins, but there is still work being done to alter the delivery profile of small-molecule drugs. One such story is that of a new dosage form for methylphenidate hydrochloride, a drug used to treat attention-deficit hyperactivity disorder (ADHD). It is the active ingredient in Novartis' brand-name drug Ritalin.

Children who take methylphenidate for ADHD have the choice of taking immediate-release tablets several times a day or a sustained-release formulation once a day. "The perception was that the sustained-release formulations weren't as effective as taking two- or three-times-a-day immediate release," says Ron Haak, senior vice president of technology development at Alza Corp., Mountain View, Calif. "Repeatedly, our pharmacologists heard the same message from leading physicians—that there must be a better delivery profile, which in fact would work as well as two- or three-times-a-day immediate-release methylphenidate."

Alza's pharmacologists identified the optimal drug delivery profile by dosing children every 30 minutes. The company's scientists then set out to engineer a tablet that provided that profile. The medication Concerta, approved by the Food & Drug Administration in early August, is the result of that effort.

The theory, according to Haak, is that a short-term tolerance builds up to methylphenidate. "If you give it continuously with a flat profile—the same concentration in the blood—the drug becomes less effective because you get a tolerance to it," Haak says. "To overcome the tolerance, we deliver the drug with a profile where there's a quick onset. It starts working right away. Then as you start getting the drug from the inside of the tablet, the concentration of the drug from the inside goes up as a function of time."



Methylphenidate hydrochloride

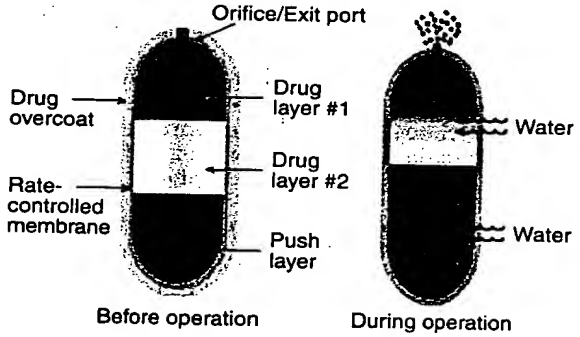
Concerta is based on Alza's Oros technology. An osmotic gradient, which can be adjusted to engineer the rate at which a drug is delivered, is established between the inside and outside of the tablet. The tablet is coated with a semipermeable membrane that controls the transport of water. The delivery time can be increased by using a thicker membrane or decreased by using a thinner one.

Concerta is made with three layers: a "push" layer and two drug layers. The push layer contains osmotically active components that expand as water enters the tablet. This expansion forces the drug out of an orifice at the top of the tablet. The tablet is also coated with an immediate-release layer of methylphenidate. After the coating dissolves, water can cross the semipermeable membrane, hydrating the interior drug layers. "The two drug layers have different concentrations, so the concentration of drug coming out of the system varies as a function of time, based on the concentrations, the pumping rate, and the mixing rate between the layers," Haak explains.

The Concerta tablet is capsule shaped—much longer than it is wide. "That gives us the ability to shut the delivery off fairly crisply," he says. "The intent was to have it turn off and match what was observed for three-times-a-day methylphenidate [so it would] not interfere with eating or sleeping."

According to Haak, the major take-home lesson f Alza's experience with Concerta is that "unless you really understand the pharmacology, you d n't nec ssarily know what the optimal delivery profile would be."

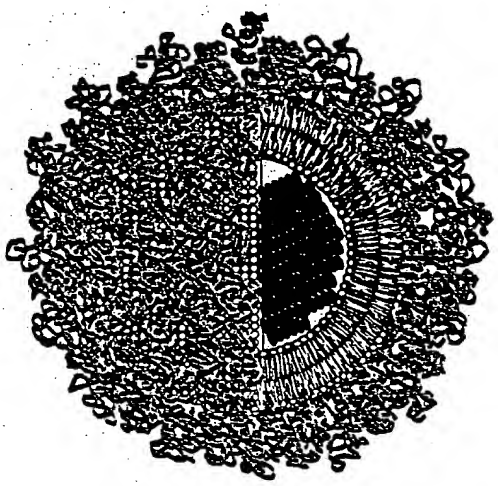
Osmotic gradient, multiple layers provide tablet's desired drug profile



sion, which is emulsified in another water phase. The result resembles a bunch of balloons inside another balloon, Willis says.

The contents of the DepoFoam particle are released through interactions with high-molecular-weight components of the interstitial fluid. The release is controlled through the choice of lipids, particularly the triglycerides, used in the membranes—high-molecular-weight triglycerides result in a slow release rate, low-molecular-weight triglycerides result in a rapid release rate, and a combination results in an intermediate release rate. Only water-soluble drugs are compatible with the DepoFoam system.

DepoFoam is designed to take the place of multiple injections, Willis says. A single administration can last two weeks to one month.



Alza's Stealth liposomes encapsulate a drug (red) in a phospholipid bilayer (blue and white). A polyethylene glycol coating (green) allows the liposomes to evade the immune system, increasing the half-life of the drug in the body.

Alza has developed what it calls Stealth liposome technology to target drugs such as anticancer agents to a specific site in the body, reducing their toxicity. Liposomes are vesicles composed of one or more concentric phospholipid bilayers. Stealth liposomes, which are coated with polyethylene glycol, are approximately 100 nm in diameter.

The coating on the liposomes allows them to evade the immune system. Thus they can achieve a circulation half-life of several days. The liposomes can be adapted for a variety of therapeutics by varying the number and composition of the lipid layers, the size and charge of the liposome, and the composition of the internal aqueous space. They can be used to deliver small molecules, proteins, peptides, and oligonucleotides. Stealth liposomes are currently on the market in the product Doxil, which is a version of the anticancer drug doxorubicin.

Alza has also developed two implantable delivery technologies called Duros and Alzamer. The Duros implant is a nonbiodegradable cylinder made of a titanium alloy. Water enters one end of the cylinder through a semipermeable membrane. The drug is forced through a port in the other end of the cylinder. The membrane controls the osmotic gradient and thus the drug delivery rate. As much as 200 mg of a drug—small molecules, peptides, proteins, genes, or other macromolecules—can be delivered over time periods as long as a year. The first product using this technology, a treatment for prostate

Getting drugs to hard-to-reach places

Areas such as the brain and the back of the eye can be difficult to reach with conventional drug delivery techniques.

One complication is that drugs must cross the blood-brain barrier before they can treat disorders in the brain. William M. Pardridge, an endocrinologist at the University of California, Los Angeles, says, "Eighty million people in the U.S. have some disorder of the brain, and more than 98% of all new drugs discovered for the brain don't cross the blood-brain barrier."

Pardridge says there is an erroneous belief that small molecules can readily cross the blood-brain barrier. But for a small molecule to cross that barrier, he says, it must meet two criteria: be less than 500 daltons and be lipid soluble. "All drugs currently in [central nervous system (CNS)] pharmaceutical practice meet those dual criteria. But the drugs that come out of high-throughput screening programs based on receptor binding are not [necessarily] going to have those [characteristics] and are not going to cross the blood-brain barrier," he points out.

One of the most important aspects of a drug delivery method to the brain is noninvasiveness, Pardridge believes. He says drilling holes in people's skulls or injecting materials into the carotid artery that force an opening in the blood-brain barrier are not appropriate options. He says blood-brain barrier delivery in the future must identify the molecular and cellular biology of endogenous blood-brain barrier transporters. "Those are the portals of entry for drugs," he emphasizes.

Pardridge has developed a "molecular Trojan horse" to move all types of molecules across the blood-brain barrier. This method, which relies on receptor-mediated transcytosis, could be used to transport drugs from small molecules all the way up to genes, Pardridge believes. In this method, the peptide from a transporter system, a modified peptide, or a monoclonal antibody that mimics the peptide is linked to the drug of interest. The two components can be linked by any of a number of drug delivery vehicles, including liposome linkers or nanoparticle technology.

The linkage must be efficient and the "chimeric peptide" must retain its bifunctionality. "The transport vector has to do its job, and the drug still has to be biologically active despite its new molecular formulation," he says.

As for the back of the eye, conditions such as diabetic retinopathy and macular degeneration could be treated if there were methods for delivering drugs.

Similar to the blood-brain barrier, the eye has the blood-vitreous barrier that prevents drugs from being delivered systemically. If drops are placed in the eyes, the drug is diluted and swept into the bloodstream before it reaches its target, says Joseph R. Robinson, a professor of pharmaceutical chemistry at the University of Wisconsin, Madison.

Robinson says several approaches are under investigation. For example, a portal could be cut in the sclera (the white outer coating) of the eye and a piece of rubber inserted that could be used to inject through. Another possibility is to inject a slowly eroding or diffusing system that would reduce the number of injections required.

Vincent H. L. Lee, a professor in the department of pharmaceutical sciences at the University of Southern California, says one way to deliver drugs to the back of the eye would be through a polymer attached to a tissue in the eye called the conjunctiva. He also says it is necessary to minimize the drugs being taken up by the bloodstream.

"You can build into a drug features that would hinder that from happening," Lee says. "What we are trying to do is increase the fraction available from 1% to 20 or 25%."

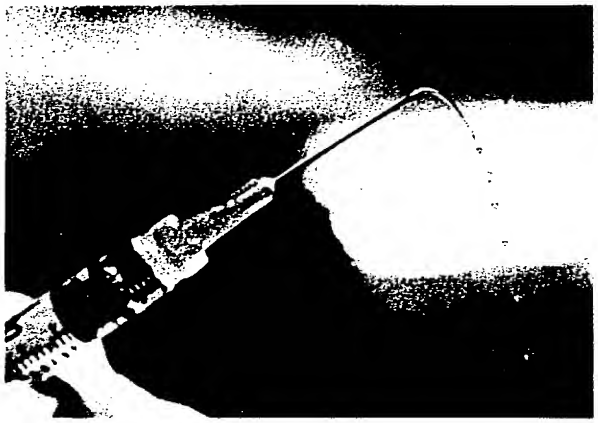
At this point, no one knows which methods will be successful. "I can tell you it's worth the effort to be able to treat blindness or conditions that lead to blindness at an earlier stage," Robinson says.

cancer, was approved by the Food & Drug Administration in March.

The Alzamer system is a biodegradable polymer that forms an implant when it is injected. The system isolates the drug from water until it is released in the body. Alzamer can provide sustained delivery of drugs for up to one month.

MacroMed, Sandy, Utah, has developed two technologies, ReGel and Oligosphere, for parenteral delivery of proteins. The ReGel system is a triblock copolymer of the type ABA, where the A blocks are poly(lactide-*co*-glycolide) and the B blocks are polyethylene glycol—both common medical polymers. The polymers form thermally reversible biodegradable hydrogels, says Gaylen M. Zentner, vice president for research and development. That means that the polymer becomes a gel as it is heated and goes back into solution as it cools.

"You can inject [the aqueous polymer solution] as a liquid. Once it hits body temperature, it becomes a gel, which is the drug-release depot. You don't have to retrieve it. It will biodegrade and be eliminated by normal processes," Zentner says.

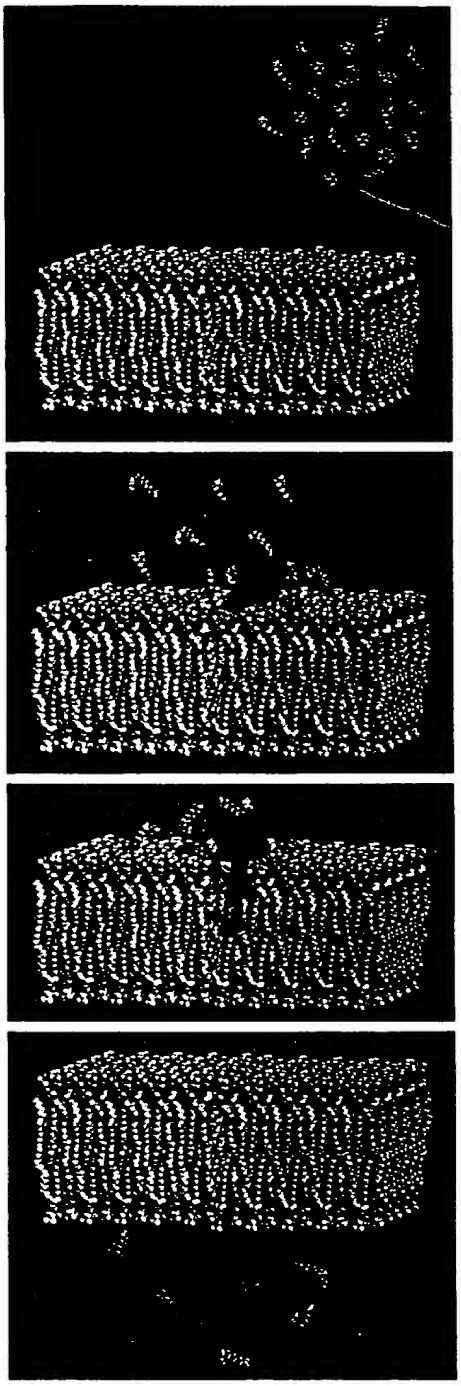


MacroMed's ReGel polymer drug delivery system, injected as a liquid, forms thermally reversible hydrogels in th body.

The gel transition temperature varies, depending on the particular polymer, anywhere from 10 to 30 °C. The polymers that gel at higher temperatures can be reconstituted, which means they can be stored as neat polymer in a formulation, Zentner says.

MacroMed uses water for the purification and formulation of its ReGel polymers. "We don't expose the proteins or other drugs to any organic solvents. That's always been a problem with other drug delivery systems—where the manufacture involves organic solvents that are pretty rough on proteins. It tends to make them aggregate. We've eliminated that by using a purely aqueous system with ReGel," Zentner explains.

Emisphere's molecular carriers (green) facilitat the transport of human growth hormone (red) across a biological membrane.



MacroMed's Oligosphere technology uses microspheres that are manufactured using an aqueous cosolvent system and a single emulsion process. Zentner says this is in contrast to more typical ways of manufacturing microspheres, which include methylene chloride solvent and double emulsions.

Zentner asserts that MacroMed's manufacturing method results in microspheres that have a more homogeneous distribution of the protein throughout the microsphere. He says this reduces the "burst effect," which is caused by a higher concentration of the protein ending up at the microsphere's surface. The material at the surface—sometimes, he says, as much as 50% of the drug—is released very quickly, often resulting in toxicity.

MacroMed's microspheres release the drug over an extended period of time, sometimes as long as several months. "Drugs that are good candidates for microspheres are drugs that are going to be chronically administered, usually parenterally administered multiple times a week for many months," Zentner says. "You can reduce that administration regimen from multiple injections every week to a single injection that lasts many months."

Alkermes has also developed two microsphere delivery technologies for injectable sustained release of drugs. Such injections would be expected to last about a month. The first, which the company calls Medisorb, is made in an emulsion-based process. The second, called ProLease, is manufactured in a cryogenic process. Both types of microspheres are made from poly(lactide-*co*-glycolide).

Medisorb is intended for use with small molecules and peptides, whereas ProLease is intended for proteins. Alkermes' Frates says the drug is evenly dispersed throughout the microspheres in both technologies. A ProLease formulation of Genentech's recombinant human growth hormone, known by the trade name Nutropin Depot, was approved by FDA in December 1999.

Oral delivery

It's hard to deny that, given the option, patients prefer to simply swallow a drug. They find that route of administration easiest and most convenient. How-

ever, for proteins and other macromolecules, the oral route is by far the hardest to accomplish.

The first challenge is simply getting the molecule past the digestive system. After all, that's precisely the kind of molecule the digestive system is intended to metabolize.

The company that is furthest along the path of developing an oral delivery method for macromolecules is Emisphere Technologies, located in Tarrytown, N.Y. Emisphere uses a carrier technology to help macromolecules survive the gastrointestinal tract.

Originally, Emisphere worked with a microsphere system, says Robert A. Baughman, senior vice president of development. However, Baughman says, "we found that the microsphere was kind of a red herring." Rather than protecting the macromolecules via encapsulation, components within the microspheres were interacting with the therapeutic compounds.

"As we began to look at the proteins and do differential scanning calorimetry, we could see that we were essentially partially denaturing the molecule," Baughman says. The melting points were shifting to lower temperatures. Carriers that didn't work in oral delivery, however, did not affect the melting points.

Successful carriers interact with macromolecules nonspecifically without forming covalent bonds. The interactions change the tertiary structure of the molecule and make it better able to cross the epithelial lipid bilayer in the intestine. However, Baughman says, "what happens at the membrane is still conjecture." Electron microscopy, immunohistochemistry, and cell and tissue delivery studies indicate that the process is passive. "We're not triggering some gated or active process," Baughman says. Known inhibitors of active transport do not retard the absorption of the compounds. Most of Emisphere's carriers are small organic molecules with a molecular weight of 250 to 350. Almost all of them are amido acids.

Emisphere's product that is closest to market is a heparin product. Heparin is a large polysaccharide that has anticoagulation properties in the blood. The carrier used with heparin is sodium *N*-[8-(2-hydroxybenzoyl)amino]caprylate, also known as SNAC. The combination is formulated as a liquid. Baughman describes heparin as "probably the most electronegative compound in the body." In the body, SNAC is also negatively charged. Baughman believes that SNAC and heparin—unlike other carrier-drug combinations—may interact by sharing a cation and forming a salt bridge.

In contrast to the predominant business model in the drug delivery industry, Emisphere is developing the SNAC-heparin combination on its own. Heparin is a generic drug that has been used for many years and is well understood in terms of its toxicology. It will demonstrate whether the delivery technology will be successful. "We made the decision that we were going to be in charge of our own destiny," Baughman says. "If the technology wasn't going to get a fair shake, we weren't doing our job." The product is in Phase III clinical trials.

Although Emisphere's technology was designed with macromolecules in mind, it can be used with a wide range of molecules, Baughman says. For example, the carriers have been shown to enable oral delivery of the small polar organic molecules disodium cromoglycate (used to stabilize mast cells so they don't release histamines) and desferox-

amine, a chelating agent used to treat the blood disease thalassemia.

However, not all molecules are suitable for Emisphere's technology. Compounds that require large doses are not going to be attractive candidates because they don't allow what Baughman calls "an elegant dosage form"—a reasonable size and number of capsules or tablets. Compounds with very low oral bioavailability that are expensive to produce aren't a good match either.

Another company working on oral dosage forms for proteins is Endorex, based in Lake Forest, Ill. Endorex's technology, called Orasomes, encapsulates proteins and other macromolecules in liposomes. Endorex is interested in applying its technology to protein and peptide-based drugs and vaccines, says Michael S. Rosen, president and chief executive officer. Rosen says the company has demonstrated the viability of its system with a number of drugs, including insulin, human growth hormone, and vaccines for tetanus and diphtheria. Thus far, all the projects are in the preclinical stage.

Unlike other liposome products that are on the market, Orasomes use polymerized liposomes. The polymerization process creates a more rigid, cross-linked structure. The Orasomes range in size from 100 to 200 nm, with the size of the particles being dictated by the molecular weight of the protein and whether it is hydrophilic or hydrophobic.

Orasomes can withstand stomach acids and phospholipase in the upper gastrointestinal tract, Rosen says. In addition, lectins attached to the surface of the Orasomes target them to the Peyer's patch, he notes, an area in the small intestine that is rich in receptor cells called M cells.

Like most drug delivery companies, Endorex is working with drugs for which another version is already on the market. "If we're working on a drug that's already been approved by FDA, we don't have to demonstrate the value of the drug," Rosen says. "We basically have to demonstrate that our version is as safe and efficacious as the injectable version. That is a lower hurdle than having to demonstrate the validity of a new chemical entity." Endorex has formed a joint venture with Elan Pharmaceutical to explore the development of the Orasomes technology for oral vaccines.

Elan is also working on macromolecule oral delivery strategies of its own. These technologies, which the company calls Promdas and Locdas, are still at

the research stage, Sternson says. However, early clinical experiments have been "encouraging."

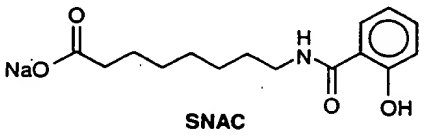
Promdas is an enhancer technology, Sternson says. "It is a proprietary system that is incorporated into traditional oral formulation presentations that transiently disrupts the gastrointestinal barrier to absorption," he explains. "The enhancer weakens the membrane for a very short period of time but long enough to allow the poorly permeable drug to be absorbed." Sternson notes that Elan has witnessed examples in clinical studies in which macromolecules with a bioavailability of less than 0.1% were increased to more than 10%.

Locdas also enhances the permeability of macromolecules, but it does so in a targeted fashion, according to Sternson. A targeting vector is combined with the drug, either through a direct linkage or by encapsulation. "The purpose of the targeting vector is to concentrate the drug in a particular region of the GI tract or to have that targeting vector be associated with a transporter in the gut," Sternson explains.

One goal for the Locdas technology is the oral delivery of vaccines. "Although [oral delivery] is very challenging, by using the technology in the vaccine area—where the amount of drug that one would actually have to deliver is considerably less than what you'd require for a therapeutic application—we increase the likelihood that we will be able to develop commercially viable products," Sternson asserts.

Poorly soluble drugs

Another drug delivery challenge is molecules that are poorly soluble in water. "We have this wonderful array of new drugs with terrible properties," the University of Wisconsin's Robinson says.



SNAC

"Forty-three percent of new chemical entities are sparingly soluble in water. It's a problem. There's a need for good drug delivery systems. These systems have to improve the therapeutic performance of the drug or in some way contribute to therapy." Such delivery systems could be used to improve drugs already on the market or to prevent candidates from falling out of the product pipeline.

Elan is addressing the problem of drug solubility with its NanoCrystal technology. The drug substance is milled into small particles less than 400 nm in diameter. The smaller particles increase the surface area of the drug and improve the dissolution of the drug in the body. The particles are in suspension, and Elan uses a proprietary stabilizer to prevent the aggregation of the small particles, Sternson says.

Most of the applications of the NanoCrystal technology require that the water be removed from the suspension to form a free-flowing powder, Sternson says. "That powder has to be stable. It has to be so stable in fact that you can subject it to the tremendous force involved in compression to make a tablet," he says. Elan has successfully prepared capsules and tablets with NanoCrystals. On Aug. 25, the first drug product incorporating NanoCrystal technology was approved by FDA for sale in the U.S.—American Home Products' Rapamune, an immunosuppressant used in kidney transplants.

Although Elan developed the NanoCrystal technology with water-insoluble small molecules in mind, it has also recently been shown to work with poorly water-soluble macromolecules, Sternson says. "We have successfully made nanoparticles of insulin and done so with a retention of the biological behavior of insulin. If you made a common subcutaneous suspension of insulin and compared it with a subcutaneously administered NanoCrystal, you would see that it fully retains its ability to lower blood glucose," Sternson claims.

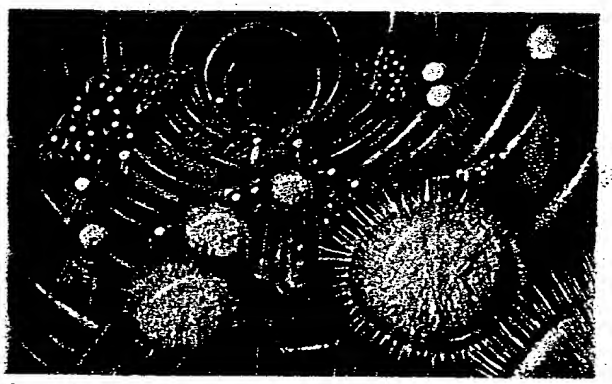
Sternson concedes that it's not yet clear what the commercial value may be of NanoCrystals for subcutaneous administration of proteins. However, he says that the demonstration "represents a proof of concept, which will lend itself to applying the NanoCrystal technology more broadly to large molecules." He suspects the technology will have value for injectable and pulmonary administration of macromolecules. Sternson says NanoCrystals should improve the efficiency of targeting macromolecules to the lung following inhalation.

Drug delivery has traditionally been used for product life-cycle management. However, Sternson claims the NanoCrystal technology is being used earlier in the process. "It is being used with increasing frequency in R&D sectors, both for clinical development candidates and at a drug discovery stage," he says.

To make NanoCrystals more attractive in a drug discovery setting, Elan has miniaturized the technology. "One of the real problems that has always prevented drug delivery from being used at early stages is that oftentimes the drug delivery scientist requires large quantities of material to apply the drug delivery technology," Sternson explains. "We can develop prototype formulations for discovery groups where we require on the order of 25 or 35 mg of materials. It's been miniaturized to accommodate the desire to use the technology at the drug discovery stage."

The need for new options for drug delivery is definitely here to stay. As Chase H&Q analyst Davis points out, "There's always going to be a big need for drugs. Drug delivery will play a crucial role in that. You have to be very careful about where in drug delivery you play. You need to climb the technological ladder and become more sophisticated with your technology."

MIT's Langer, who has long been involved in the drug delivery field, says: "I'm very excited by the fact that the first protein delivery systems are coming on the market and that a lot of protein delivery systems and novel delivery systems are moving into the clinic. I've been involved in the area for almost 30 years, with people saying that these things will never work or they'll never be in the clinic or never make any money or never make any products. Now we see that's not the case. It's a validation of something that I and other people have fought long and hard for."◀


An artist's representation of End rex's liposom s, called Orasom s (green), passing through the small intestine and binding t clust rs of re pt r cells. Ea h Orasom contains a prot in-bas d drug r vaccin .